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INTERFERON-ALPHA TREATMENT RESULTS IN THE DEPLETION OF DORMANT JAK2-MUTANT HSC IN A MURINE MODEL OF POLYCYTHEMIA VERA

Topic: 15. Myeloproliferative neoplasms - Biology & Translational Research

Keywords: Fedratinib | Hematopoietic stem cell | Interferon alpha | Myeloproliferative disorder

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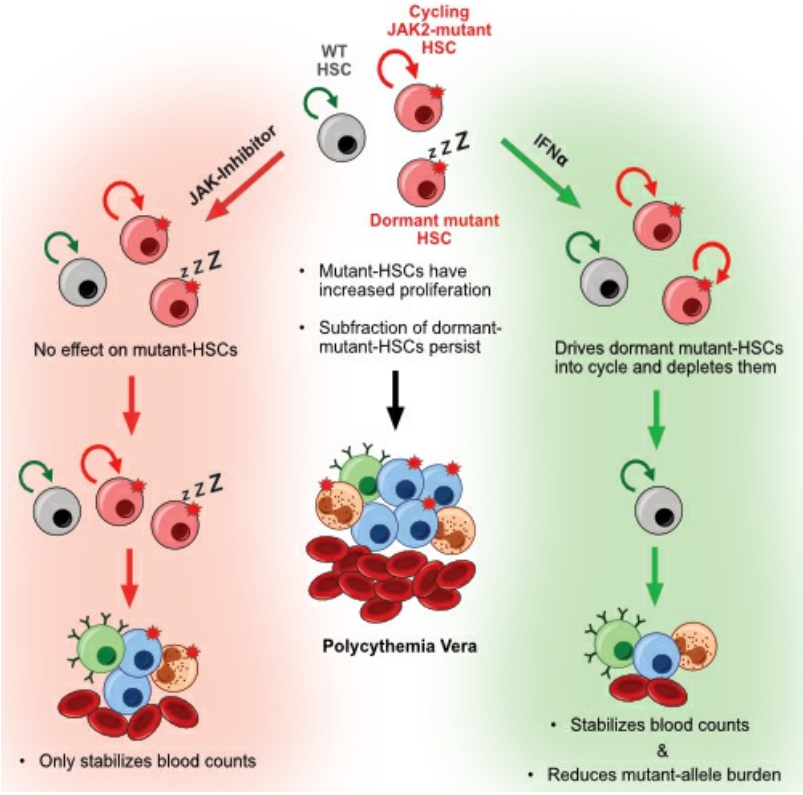
Background: The majority of patients with *Bcr-Abl* negative myeloproliferative neoplasms (MPN) have a JAK2-V617F mutation. Targeted therapy with JAK-inhibitors have been shown to normalize blood parameters but do not lead to a significant reduction in the mutant allelic burden. Interferon-alpha (IFNα) therapy is the only treatment option available that can achieve molecular remission. However, long-term treatment with IFNα is required and patients frequently exhibit adverse side-effects. Thus it is important to elucidate the mechanism of action of IFNα in achieving molecular remission, which is still not completely understood. Previous studies in JAK2-mutant MPN mouse model have shown that IFNα treatment leads to the depletion of the mutant hematopoietic stem cells (HSCs). Our previous findings have shown that IFNα can drive wildtype dormant HSCs into cell cycle, leading to attrition of functional HSCs. We hypothesize that IFNα treatment eliminates the functional disease-propagating JAK2-mutant HSCs by breaking their dormant status.

Aims: To assess the inherent proliferative index of JAK2-mutant HSCs and the effect of IFNα treatment on mutant-HSC dormancy in comparison to JAK-inhibitor treatment.

Methods: A BrdU pulse-chase experiment was performed on a JAK2-V617F mouse model of MPN, to assess the inherent proliferation of JAK2-mutant HSCs. The dilution of BrdU-label in the mutant HSCs was assessed at different time-points post BrdU-pulse. To further compare the effects of IFN-α and Fedratinib (JAK-inhibitor) on dormant mutant HSCs, mice exhibiting MPN symptoms were pulse-labelled with BrdU as before. The mice were then treated with pegylated-IFNα (600ng or 300ng) or Fedratinib (120mg/kg) for 4 weeks. The proportion of BrdU-label-retaining HSCs in the bone marrow and the changes in blood parameters were assessed 48 hours after final treatment.

Results: The dilution of BrdU-label was observed to be faster in the JAK2-mutant HSCs compared to wildtype-HSCs during disease progression, indicating that JAK2-mutant HSCs have increased cycling and proliferation. However, a sub-fraction of dormant BrdU-label-retaining mutant HSCs were still observed after 20 weeks of chase. While both Fedratinib and peg-IFNα treatment was observed to stabilize blood parameters in the JAK2-mutant mice, only peg-IFNα was observed to significantly reduce the mutant allelic burden in the peripheral blood and eliminate the BrdU-positive dormant mutant HSCs.

Image:



Summary/Conclusion: JAK2-mutant HSCs have an inherently higher cycling compared to wildtype-HSCs. However, we identify for the first time a dormant sub-fraction of mutant HSCs within the bone marrow. These dormant HSCs may be responsible for disease propagation and relapse after therapy. In support of this, dormant HSCs were unaffected by Fedratinib treatment in mice where hematologic parameters had been normalized, while peg-IFNα was found to eliminate the dormant mutant HSCs. These data provide a new model to explore novel strategies to eliminate therapy resistant HSCs in the setting of JAK2 mutated MPNs.

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